selected from halo, C_1-C_6 alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N((C_{1-6})alkyl)_2$] halo, C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$ OH and C_{1-3} alkylenedioxy, or

a 5-or 6-membered heteroaryl ring containing up to 4 heteroatoms selected from N, O and S, which group is optionally substituted by one or more groups selected from C_{1-6} alkyl [which may itself be substituted by one or more substituents selected from halo, C_1-C_6 alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N((C_{1-6})alkyl)_2$], halo,C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

the formulation characterized in that it is adapted for administration to a companion animal.

R^3 cont.

11. (amended) A formulation according to claim 10, which is adapted for oral administration and has a taste attractive to the companion animal.

In the Drawings

Please insert Figure 1, attached to this response.

Remarks

Claims 1-11 are pending in the application. Claims 12-14 have been cancelled. The specification is objected to as containing an illustration which does not come within the purview of 37 CFR 1.58(a). The chart on page 15 of the specification has been deleted, and the chart has been submitted as Figure 1. No new matter has been added. The specification has further been amended to include a section entitled "Brief Description of the Drawings."

Claims 1-9 stand rejected under 35 USC § 101 as being drawn to non-statutory subject matter. Claims 10-14 are objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claims, and claims 10-14 stand rejected under 35 USC § 103(a) as being unpatentable over Harada et al. EP 0882719 and Harada et al WO 98/57938.

Reconsideration is requested in view of the remarks below.

Rejection of Claims 1-9 under 35 USC § 101

Claims 1-9 stand rejected under 35 USC § 101 as being directed to non-statutory subject matter. Claims 1-9 have been amended to comply with the requirements of 35 USC § 101. Reconsideration and examination of claims 1-9 is respectfully requested.

Objection of claims 10-14 under 37 CFR 1.75(c)

Claims 10-14 are objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 10-14 have been amended to incorporate the limitations claim 1, in particular the compound recited therein. Reconsideration and withdrawal of the objection is respectfully requested.

Rejection of claims 10-14 under 35 USC § 103(a) as being unpatentable over Harada et al. (EP 0 882 719 [Harada et al '719] and Harada et al. (WO 98/57938)[Harada et al. '938]

Claims 10-14 stand rejected under 35 USC § 103(a) as being unpatentable over Harada et Harada et al '719 and Harada et al. '938. Reconsideration and withdrawal of the rejection is requested in view of the following remarks.

The examiner asserts on page 4 of the office action that the Applicants' claimed subject matter would have been obvious as the cited references teach that the compounds are effective for treating endothelin mediated disorders and the selection of a specific host in which to practice such treatment would have been a matter well within the purview of the skilled artisan.

"A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art." If the Examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Rijckaert, 9 F.3d 1531, 28 USPQ2d 1955,1956(Fed. Cir. 1993)

Applicants submit that the Examiner has not established a prima facie case in this instance. Contrary to the Examiner's position, Harada et al '719 and Harada et al '938 fail to disclose or suggest that compounds of formula I, as defined by the Applicants, have a longer duration of action. This provides the advantage that the compounds of formula I have a longer duration of action and the frequency with which they must be administered may be

reduced.

As stated on page 2 of the application, lines 19-21, in the present invention it has been found that a small group of endothelin receptor antagonist compounds are particularly useful in the treatment of endothelin-mediated disorders in companion animals. As shown in the pharmokinetic studies on pages 5 through 9 of the application, compounds X and Y, as disclosed in the specification, were evaluated by comparison to two compounds, including Example 2 of Harada '938. As shown in the table at the bottom of page 8, only compounds X and Y would still be efficacious after 24 hours following a 2.0 mg/kg i.v dose, as they would be present at 100% of the K_b value or more.

There is no disclosure or suggestion in Harada et al '719 or Harada et al '938, that compounds of formula I, as defined by the Applicants, would possess the aforementioned advantages. It is the Examiners' duty to explain the specific understanding or principle within the knowledge of the skilled artisan that would motivate one with no knowledge of the Applicants' invention to select the compounds of formula I, as defined by the Applicants, to provide treatment to companion animals, the treatment having the advantages described in the specification.

Accordingly, it is submitted that the Examiner has not set forth a prima facie case of obviousness under 35 USC § 103. Reconsideration and withdrawal of the rejection of claims 10-14 under 35 USC § 103(a) as being unpatentable over Harada et Harada et al '719 and Harada et al. '938 is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by current amendment. The attached page is captioned "Version with Markings to Show Changes Made." Early allowance of the claims is respectfully requested.

Respectfully submitted,

Date: 8-13-02

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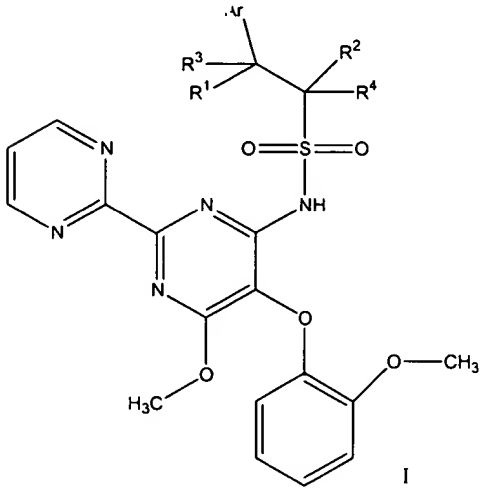
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1 [The use of a compound of formula I] A method for the treatment or prophylaxis of an endothelin-mediated disorder in a companion animal which comprises administering an effective amount of a compound of formula I or a veterinarily acceptable salt thereof to the companion animal, the compound of formula 1 having the formula:



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wherein R^1 and R^2 each represent H, or together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

when R^1 and R^2 each represent H, then R^3 and R^4 also represent H;

when R^1 and R^2 together represent a second carbon-carbon bond between the carbon atoms to which they are attached, then R^3 and R^4 independently represent H or C_1-

C_6 alkyl;

Ar represents:

phenyl or naphthyl, which groups are optionally substituted by one or more groups selected from C_1-C_6 alkyl [which may itself be substituted by one or more substituents selected from halo, C_1-C_6 alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N((C_{1-6})alkyl)_2$] halo, C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$ OH and C_{1-3} alkylenedioxy, or

a 5-or 6-membered heteroaryl ring containing up to 4 heteroatoms selected from N, O and S, which group is optionally substituted by one or more groups selected from C_{1-6} alkyl [which may itself be substituted by one or more substituents selected from halo, C_1-C_6 alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N((C_{1-6})alkyl)_2$], halo,C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl$)_2$;
[or a veterinarily acceptable salt thereof.]

2. [The use as claimed in claim 1] A method according to claim 1, wherein the companion animal is a cat, a dog or a horse.

3. [The use as claimed in claim 1 or claim 2] A method according to claim 1 or 2, wherein the endothelin mediated disorder is hypertension, congestive heart failure or chronic renal failure.

4. [The use as claimed in any one of the preceding claims] A method according to claim 1, wherein R^1 and R^2 each represent H.

5. [The use as claimed in any one of the preceding claims] A method according to claim 1, wherein R^3 and R^4 each represent H.

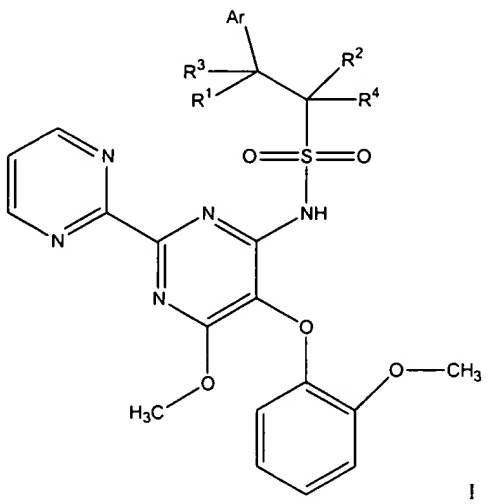
6. [The use as claimed in any one of the preceding claims] A method according to claim 1 wherein Ar represents phenyl, napththyl, or thienyl, which groups are optionally substituted by one or more groups selected from C_{1-6} alkyl, halo, CF_3, C_{1-6} alkoxy, CO_2H and C_{1-6} alkoxycarbonyl.

7. [The use as claimed in any one of the preceding claims] The method according to claim 1, wherein Ar is phenyl.

8. [The use as claimed in any one of the preceding claims] The method of claim 1, wherein the endothelin mediated disorder is congestive heart failure.

9. [The use as claimed in any one of claims 1 to 7] The method of claim 1, wherein the endothelin mediated disorder is chronic renal failure.

10. A formulation containing a compound of formula I [as defined in claim 1] or a veterinarily acceptable salt thereof:



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wherein R^1 and R^2 each represent H, or together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

when R^1 and R^2 each represent H, then R^3 and R^4 also represent H;

when R^1 and R^2 together represent a second carbon-carbon bond between the carbon atoms to which they are attached, then R^3 and R^4 independently represent H or C_1-C_6 alkyl;

Ar represents:

phenyl or naphthyl, which groups are optionally substituted by one or more groups selected from C_1-C_6 alkyl [which may itself be substituted by one or more substituents selected from halo, C_1-C_6 alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N((C_{1-6})alkyl)_2$] halo, C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$ OH and C_{1-3} alkylenedioxy, or

a 5-or 6-membered heteroaryl ring containing up to 4 heteroatoms selected from N, O and S, which group is optionally substituted by one or more groups selected from C_{1-6} alkyl [which may itself be substituted by one or more substituents selected from halo, C_1-C_6 alkoxy, CO_2H, NH_2, $NH(C_{1-6}$ alkyl) and $N((C_{1-6})alkyl)_2$], halo,C_{1-6} alkoxy, CO_2H, C_{1-6} alkoxycarbonyl, NO_2, CN, NH_2, $NH(C_{1-6}$ alkyl), and $N(C_{1-6}$ alkyl)$_2$;

the formulation characterized in that it is adapted for administration to a companion animal.

11. (amended) A formulation [according to] as claimed in claim 10, which is adapted for oral administration and has a taste attractive to the companion animal.

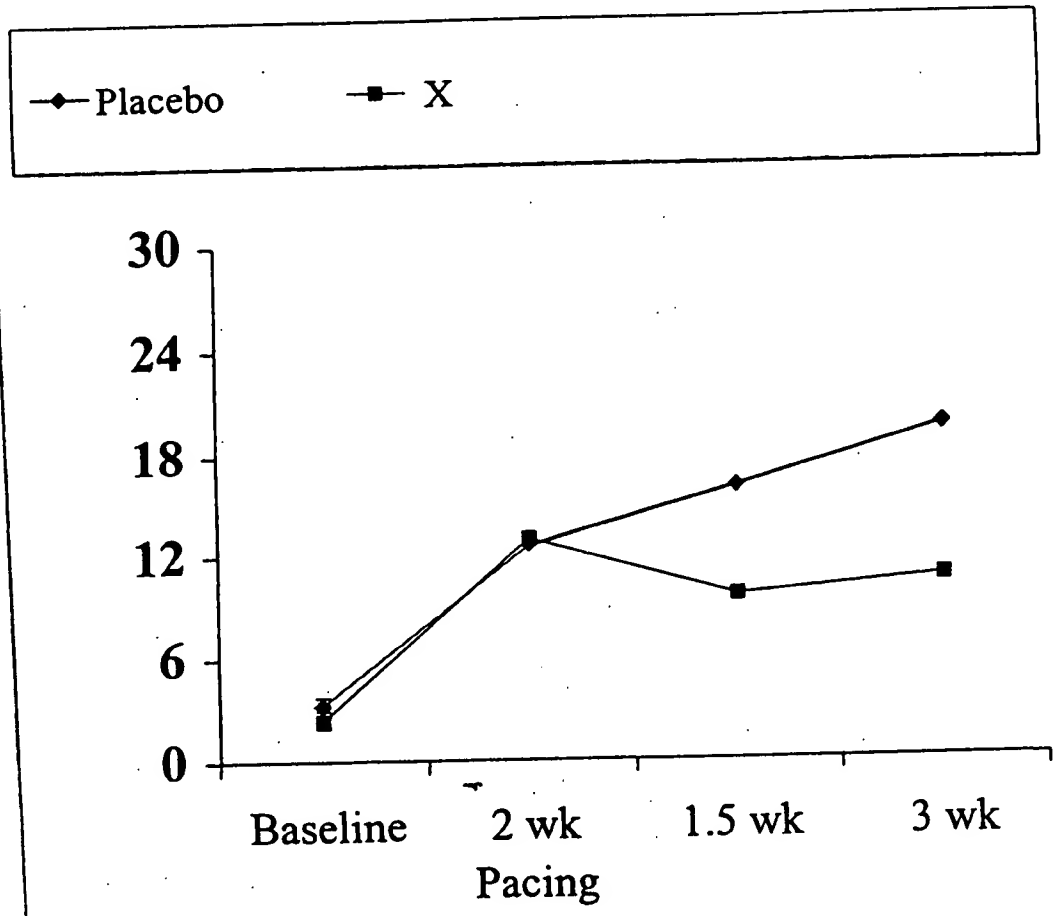

Figure 1

... QHF and then assigned to oral gavage